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Synthesis and molecular structure of spirocyclic 2-oxindole derivatives of 2-amino-4*H*-pyran condensed with the pyrazolic nucleus

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Abstract—4,3′-Spiro[(6-amino-5-R-3-methyl-2*H*,4*H*-pyrano[2,3-*c*]pyrazolo)-2′-oxindoles] were synthesized based on the three-component condensation of isatins with 3-methyl-pyrazolone-5 and respective methylene active nitriles in the presence of basic catalysts. The molecular structure of the resulting compounds was proved unambiguously by X-ray diffraction.

1. Introduction

Condensed heterocyclic compounds containing a 2-oxindole nucleus or a 4*H*-pyrano fragment have different pharmacological activities, e.g., spirocyclic 2-oxindole systems form the basis of such alkaloids as alstonisine **1** and macroxin **2** from the plants of the *Alstonia*[1,2] genus and bisindole spirocyclic alkaloids from the group of gardmultine, e.g., **3** from *Gardneria multiflora*[3] having an antimalarial and ganglioblocking action (Chart 1).

This work is devoted to the synthesis of 4,3′-spiro[(6-amino-5-R-3-methyl-2,4-dihydro-pyrano[2,3-*c*]pyrazolo)-2′-oxindoles] **4** as templates for discovering new analogues of the melatonine hormone **5** and its endogenous precursor serotonine **6**. Both **5** and **6** contain the pyrano[2,3-*c*]pyrazol system, and the aminoethyl fragment is structurally attached to the pyranic cycle (Chart 2). We also intended to study the molecular structure of the target compounds.

Indoleless analogues of the hormone melatonine[4] were found among 4*H*-pyran derivatives. Condensed pyrano[2,3-*c*]pyrazol can inhibit selectively the A_2-subtypes of adenosine receptors[5] and some of them also have herbicidal properties.[6] Addition of carbonyl compounds to electron-deficient ethylenes (to 3-cyanomethylidene-2-oxindoles in the Michael reaction) can serve as a suitable approach to the synthesis of such tetracyclic 2-oxindole systems.[7,8] Indeed, the application of appropriate heterocyclic compounds to the reaction as the carbonyl component affords different condensed

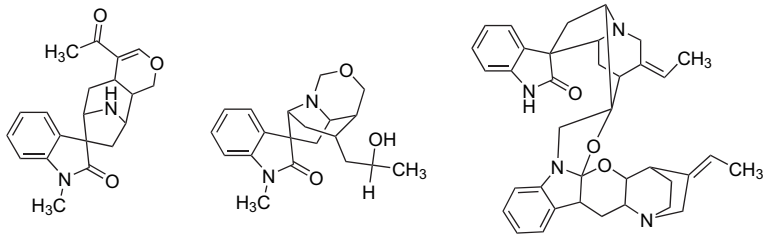

Chart 1.

Keywords: 3-Spiro-2-oxindoles; Pyrano[2,3-*c*]pyrazol; Methylene active nitriles; Michael reaction; X-ray diffraction analysis.
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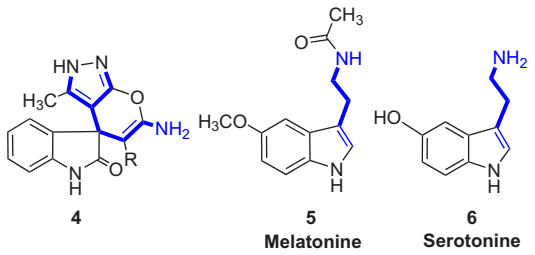


Chart 2.

Table 1. Yields for the synthesized compounds **4a–h**

Compounds	R^1	R^2	Yields, %	
			Method A	Method B
4a	H	H	74	68
4b	Me	H	72	56
4c	Bn	H	65	57
4d	H	Me	57	48
4e	H	H	61	54
4f	Me	H	63	51
4g	Bn	H	67	49
4h	H	Me	55	43

derivatives of 2-amino-4*H*-pyran condensed featuring heterocyclic nuclei.[9,10] Previously the synthesis of pyrano[2,3-*c*]pyrazol systems using aliphatic [11,12] and aromatic aldehydes has been reported.[13] However, the problem of regioselectivity in the interaction between 3-cyanomethylidene-2-oxindoles and 3-methylpyrazolone was unsolved in these reports.

2. Results and discussion

Herein we introduce a method of obtaining novel 4,3′-spiro[(6-amino-5-R-3-methyl-2,4-dihydro-pyrano[2,3-*c*]-pyrazolo)-2′-oxindoles] **4** from the three-component condensation of isatins **7**, a suitable CH acid (malonodinitrile **9** or cyanoacetic ester **10**) and 3-methylpyrazolone-5 **8**.

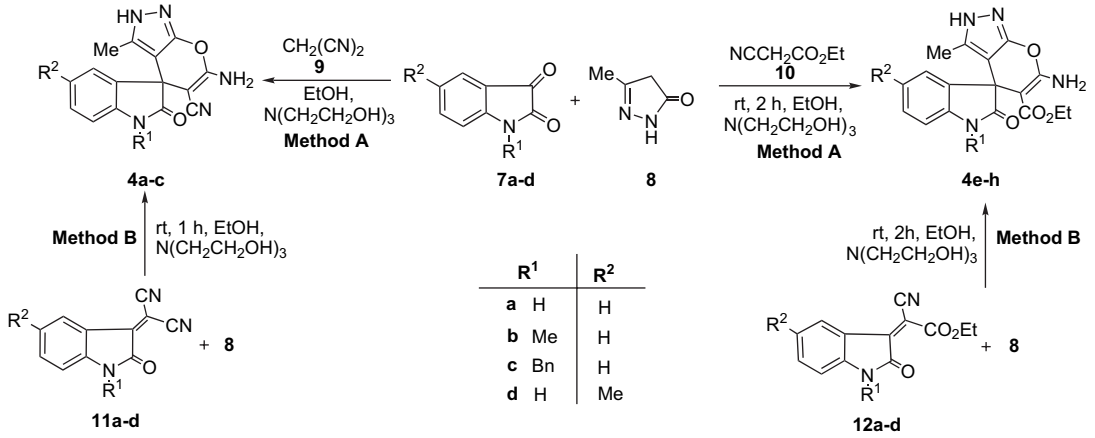
The reaction of equimolar quantities of compounds **7**, **9** and **8** for a short duration in boiling ethanol in the presence of triethanolamine results in the formation of the desired spiro-2-oxindole derivatives of pyrano[2,3-*c*]pyrazol **4a–c** (Scheme 1).

The use of cyanoacetic ester **10** instead of dinitrile **9** in the three-component condensation with isatins **7** and pyrazolone **8** in the presence of triethanolamine yields **4e–h** in 55–74% but requires a longer reaction time (Scheme 1, Table 1).

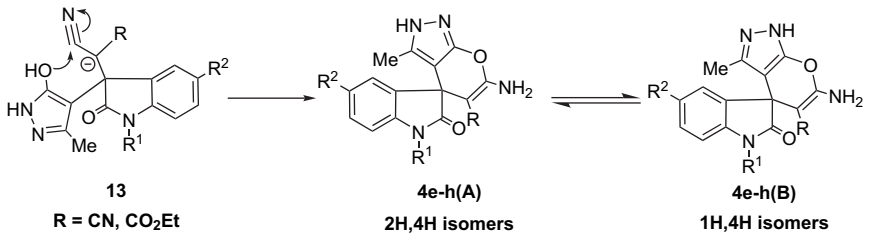
3-Cyanomethylidene-2-oxindoles **11** and **12** were prepared via Knovenagel condensation of the corresponding isatins **7a–d** and methylene active nitriles **9** or **10** in the presence of a basic catalyst as reported in the literature.[14,15,18] The addition of **8** to the substituted 3-cyanomethylidene-2-oxindoles **11** and **12** takes place under boiling in ethanol in the presence of triethanolamine for 30 or 40 min and also affords the target compounds **4a–h** in 43–74% yield (Scheme 1, Table 1). Apparently, both the methods involve the formation of Michael adducts **13**, which are regioselectively cyclized into pyrano[2,3-*c*]pyrazol **4a–h** in spite of evident steric hindrance. At the same time, the structure of compounds **4a–h** does not come into conflict with either **4A** or its prototropic isomer **4B** (Scheme 2).

Compounds **4a–h** we obtained were stable and analytically pure colourless powders that could be recrystallized from the ethanol and DMF mixtures. The infrared spectrum of the compounds features absorption bands of valence and deformation oscillations of amino, cyano or carbethoxy groups.

^{1}H NMR spectrums of **4a–h** compounds feature a characteristic set of signals: an extended high-intensity singlet of α-amino group of the pyranic cycle at 8.0–8.3 ppm, aromatic protons of the 2-oxindole system at 6.8–7.5 ppm, and the proton signal of the NH group of the pyrazolic ring in the form of a singlet at 12.0–12.3 ppm. The corresponding non-alkylated compounds **4a**, **d**, **e**, **h** (R_1=H) also feature a proton singlet from the NH group of the 2-oxindole ring in a higher field at 10.5–10.8 ppm. A singlet can be observed in all of the compounds at 1.2–1.5 ppm corresponding to the methyl group of the pyrazolic ring. Protons from the NH group of the pyrazolic and 2-oxindole rings as well as of the α-amino group of the pyranic cycle can be easily exchanged in the presence of D_2O in DMSO-d_6 solution.



Scheme 1.



Scheme 2.

Also the ^{13}C NMR spectra confirmed the structures of the all synthesized compounds. Furthermore, full assignment of the ^{13}C NMR data confirmed the structures **4**, where the key signal at δ 167–177 ppm was assigned to the 2-oxindolic carbonyl group; at δ 55 ppm was assigned to the quaternary sp^3 carbon; at δ 154–155 and δ 162 ppm was assigned to the sp^2 β- and α-carbons of pyranic ring. The signal at δ 118 ppm was assigned to the nitrile carbon in the pyranic ring for compounds **4a–c**. Full spectral data for all new compounds are presented in Section 4.

Thus, based on the data it is not possible to establish unambiguously to which of the tautomeric structures (**A** or **B**) the resulting compounds correspond. To establish the regioselectivity of the condensation of isatins **7** in the three-component condensation with pyrazolone **8** and CH acids **11** and **12**, and definitively confirm the structure of **4a–g**, 4,3′-spiro[(6-amino-5-cyano-3-methyl-2*H*,4*H*-pyrano[2,3-*c*]pyrazolo)-*N*′-benzyl-2′-oxindole] **4c** (Fig. 1) and 4,3′-spiro[(6-amino-5-carbethoxy-3-methyl-2*H*,4*H*-pyrano[2,3-*c*]pyrazolo)-*N*′-methyl-2′-oxindole] **4f** (Fig. 2) were examined by X-ray diffraction of single crystals.

The dihydroindolone fragment is planar within 0.02 Å in the **4c** and **4f** molecules. The spirojoined dihydroindolone and imidazodihydropyrane bicycles are arranged almost orthogonally with respect to each other, the angle between their mean planes is 89.9° for **4f** and 88.0° for **4c**. The plane of dihydropyrane ring and ester substituent in molecule **4f** are coplanar within 0.03 Å. Such conformation of the substituent is stabilized by an intramolecular hydrogen bond: N(4)–H(4Na)···O(3) H···O 1.90 Å (N–H···O 143°). However, compared to **4f**, the dihydropyran ring in molecule **4c** adopts a flattened chair conformation. Deviation of the C(7) atom from the mean plane of remaining atoms of the ring is 0.18 Å. Unlike the earlier investigated compounds **7**[12] and **8**[13] (Fig. 3), the lengths of the O(2)–C(12) and O(2)–C(13) bonds in the molecules **4f** and **4c** are not equivalent: 1.353(2) Å and 1.371(2) Å, correspondingly for **4f** and 1.356(1) Å and 1.366(2) Å for **4c**.

The phenylic radical in the molecule **4c** has near from orthogonal orientation relatively the plane of the dihydroindolone fragment (the C(1)–N(1)–C(16)–C(17) torsion angles is 78.7(2)°) and it is turned relatively the N(1)–C(16) bond (the N(1)–C(16)–C(17)-C(22) torsion angles is 70.8(2)°).

In the crystal phase molecules **4f** form the infinitive chains along the (110) crystallographic direction due to the intermolecular hydrogen bonds: N(2)–H(2N)···O(1)′ (1−*x*, 1−*y*, 1−*z*) H···O 2.09 Å N–H···O 152° and N(4)–H(4Nb)···N(3)′ (1−*x*, 2−*y*, 1−*z*) H···N 2.32 Å N–H···N

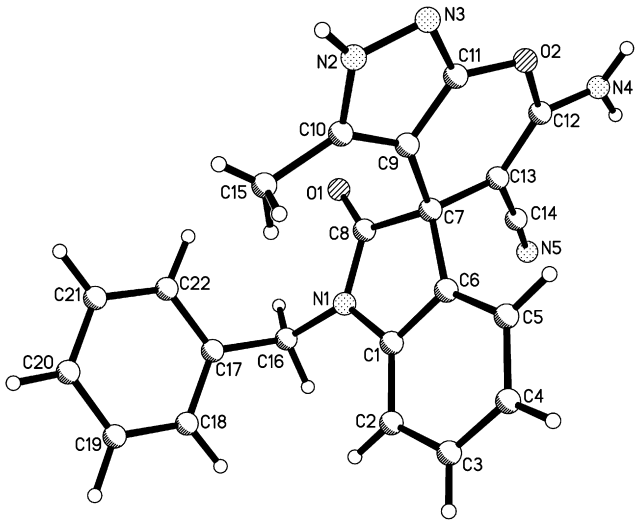


Figure 1. The molecular structure of compound **4c**.

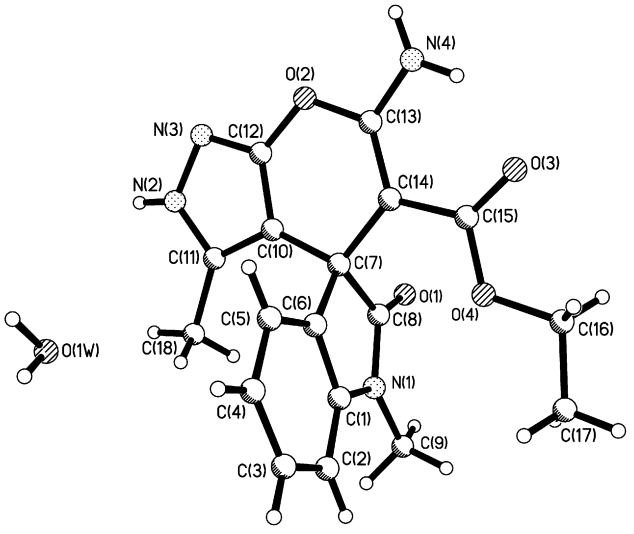


Figure 2. The molecular structure of compound **4f**.

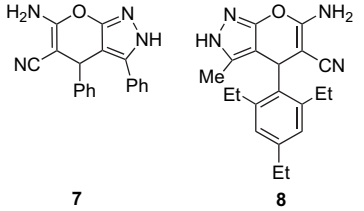


Figure 3. The earlier investigated compounds **7** and **8**.

174°. Molecule **4c** forms centrosymmetric dimers in the crystal phase due to the intermolecular hydrogen bond: N(4)–H(4Na)···N(3)′ (−*x*, 1−*y*, 1−*z*) H···N 2.25 Å N–H···N 164°. The dimers are bounded by intermolecular hydrogen bonds: N(2)–H(2N)···N(5)′ (*x*, 0.5−*y*, 0.5+*z*) H···N 2.07 Å N–H···N 165° and N(4)–H(4Nb)···O(1)′ (−*x*, 0.5+*y*, 0.5−*z*) H···O 2.37 Å N–H···O 162°.

3. Conclusion

Spiro-2-oxindole derivatives of pyrano[2,3-*c*]pyrazol **4** were synthesized based on a three-component one-pot procedure. Using nitrile **4c** and ether **4f** as representative examples, it was established that the resulting compounds exist in the solid state in the form of 2*H*,4*H* isomers but not in the form of prototropic 1*H*,4*H* isomers. The differences between the C–O bonds within the C–O–C fragment of the dihydropyrane ring were established for the first time.

4. Experimental section

4.1. General

Starting materials were obtained from commercial suppliers and used without further purification. Melting points were obtained on a Gallenkamp melting point apparatus, Model MFB-595 in open capillary tubes. ^{1}H NMR spectra were recorded on a Varian WXR-400 (200 MHz) spectrometer in DMSO-d_6 using TMS as an internal standard (chemical shifts in parts per million). ^{13}C NMR spectra were recorded on a Varian GEMINI-400 (100.61 MHz), the references at the signal of the solvent 39.5 ppm for DMSO-d_6. IR spectra were taken on a Specord M-82 spectrophotometer in KBr pellet. Elemental analyses were carried out using Carlo Erba CHNS-O EA 1108 analyzer. Mass spectra were taken on a Varian 1200 L DIP (EI, 70 eV).

4.2. X-ray diffraction study

4.2.1. Crystal data for 4c. The crystals of **4c** ($C_{22}H_{17}N_5O_2$) are monoclinic. At 293 K a=8.887(1), b=11.137(1), c=19.244(1) Å, β=94.15(1)°, V=1899.5(1) Å^3, M_r=383.41, Z=4, space group $P2_1/c$, d_{calcd}=1.341 g/cm^3, μ(Mo Kα)=0.090 mm^{-1}, F(000)=800. Intensity of 12,755 reflections (4310 independent, R_{int}=0.020) was measured using the 'Xcalibur-3' diffractometer (graphite monochromated Mo Kα radiation, CCD detector, ω-scaning, $2\theta_{max}$=55°). The structure was solved by direct method using SHELXTL package.[16] Positions of hydrogen atoms were located from electron density difference maps and refined within isotropic approximation. Full-matrix least-squares refinement against F^2 within anisotropic approximation for non-hydrogen atoms using 4223 reflections was converged to wR_2=0.118 (R_1=0.040 for 2703 reflections with $F>4\sigma(F)$), S=0.955). Atomic coordinates and crystallographic parameters have been deposited with the Cambridge Crystallographic Data Centre (CCDC 643527).

4.2.2. Crystal data for 4f. The crystals of **4f** ($C_{18}H_{18}N_4O_4$) are triclinic. At the 293 K a=9.019(2), b=10.232(2), c=11.593(2) Å, α=74.53(2)°, β=67.13(2)°, γ=67.87(2)°, V=904.0(3) Å^3, M_r=717.74, Z=2, space group $P\overline{1}$, d_{calcd}=1.318 g/cm^3, μ(Mo Kα)=0.096 mm^{-1}, F(000)=377. Intensity of 5270 reflections (3112 independent, R_{int}=0.015) was measured using 'Xcalibur-3' diffractometer (graphite monochromated Mo Kα radiation, CCD detector, ω-scaning, $2\theta_{max}$=50°). The structure was solved by direct method using SHELXTL package.[16] Positions of hydrogen atoms were located from electron density difference maps and refined by 'riding' model with $U_{iso}=nU_{eq}$ of non-hydrogen atom bonded with the given hydrogen atom (n=1.5 for methyl and hydroxyl groups and n=1.2 for other hydrogen atoms). Full-matrix least-squares refinement against F^2 in anisotropic approximation using 2958 reflections was converged to wR_2=0.156 (R_1=0.054 for 2240 reflections with $F>4\sigma(F)$), S=0.965). Atomic coordinates and crystallographic parameters have been deposited with the Cambridge Crystallographic Data Centre (CCDC 643526).

4.3. General procedure for the synthesis of 3-cyanomethyliden-2-oxindoles 11a–d and 12a–d

To a solution of the appropriate isatins **7a–d** (0.01 mol) in dry ethanol (20.0 mL) malonodinitrile **9** (0.66 g, 0.01 mol) or the cyanoacetic acid ethyl ester **10** (1.1 mL, 0.01 mol) was added, as well as 1.3 mL (0.01 mol) of triethanolamine as catalyst. When methylene active nitrile **9** was used the reaction mixture was mixed at room temperature until precipitation of compounds (**11a–d**) was obtained.[17] Otherwise, the reaction mixture was heated to nearly 2 h, and after allowing the mixture to cool to room temperature, crystalline products of **12a–d** precipitated. The precipitated solids of compounds **11a–d** and **12a–d** were filtered off and washed several times with cold ethanol (20 mL) to afford analytically pure compounds (**11a** mp 143–145 °C, **11b** mp 148–150 °C, **12a** mp 173–175 °C, **12b** mp 190–193 °C, with ca. 90% yields).[14,15,18]

4.3.1. 2-(1-Benzyl-2-oxo-1,2-dihydro-indol-3-ilidene)-malononitrile (11c). Fine dark-red needles, mp 200–203 °C; 2.56 g (90%) yield. Found: C, 75.59; H, 3.85; N, 14.70. $C_{18}H_{11}N_3O$ requires C, 75.78; H, 3.89; N, 14.73%; ν_{max} (KBr) 3030, 2227, 1719, 1612, 1592, 1496, 1469 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 4.93 (s, 2H), 7.05–7.95 (m, 9H); δ_C (100.61 MHz, DMSO-d_6) 42.958 (NCH_2), 81.543 (ilidene sp^2 carbon $=C(CN)_2$), 118.123 (2C, CN), 110.815, 111.840, 112.812, 123.424, 125.539, 127.230, 127.550, 128.540, 135.052, 137.331, 146.960, 149.390 (sp^2 carbons), 162.461 (CO 2-oxindolic); MS (EI) *m*/*z* 285 (57 M$^+$), 257 (2.3), 166 (9.6), 126 (45.0), 91 (95), 89 (3.5), 65 (11.9%).

4.3.2. 2-(5-Methyl-2-oxo-1,2-dihydro-indol-3-ilidene)-malononitrile (11d). Fine red solid, mp 185 °C; 1.86 g (89%) yield. Found: C, 68.70; H, 3.26; N, 20.06. $C_{12}H_7N_3O$ requires C, 68.89; H, 3.37; N, 20.09%; ν_{max} (KBr) 3257, 3108, 2231, 2110, 1731, 1620, 1584, 1466, 1341 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 3.42 (s, 3H), 6.98–7.1 (m, 3H), 11.25 (s, 1H); δ_C (100.61 MHz, DMSO-d_6) 25.453 (5-CH_3), 83.940 (ilidene sp^2 carbons $=C(CN)_2$), 117.958 (2C, CN), 123.245, 126.723, 127.130, 128.650, 132.529, 134.325, 149.450 (sp^2 carbons), 162.840 (CO 2-oxindolic); MS (EI) *m*/*z* 209 (75 M$^+$), 159 (5.6), 135 (3.2), 91 (32), 62 (12%).

4.3.3. (1-Benzyl-2-oxo-1,2-dihydro-indol-3-ilidene)-cyanoacetic acid ethyl ester (12c). Fine dark-red solid, mp

225 °C; 1.82 g (71%) yield. Found: C, 65.44; H, 4.70; N, 10.98. $C_{20}H_{16}N_2O_3$ requires C, 65.62; H, 4.72; N, 10.93%; ν_{max} (KBr) 3028, 2227, 2213, 1719, 1622, 1578, 1469 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 1.35 (3H, t, *J* 7.2 Hz), 2.52 (2H, q, *J* 3.9 Hz), 4.90 (s, 2H), 7.10–7.95 (m, 9H); δ_C (100.61 MHz, DMSO-d_6) 13.599, 58.768 (Et carbons), 43.125 (NCH_2), 106.235 (ilidene sp^2 carbon $=C(CN)_2$), 117.548 (2C, CN), 120.342, 124.524, 126.530, 126.938, 127.123, 128.480, 135.830, 142.450, 164.512 (sp^2 carbons), 162.300, 162.282 (CO sp^2 carbons); MS (EI) *m/z* 332 (88 M^+), 304 (12), 257 (21), 288 (4.2), 287 (2.8), 262 (5.6), 261 (9.8), 249 (10), 237 (15), 234 (2.3), 226 (1.5), 177 (6.8), 153, 92 (12), 90 (13), 65 (14%).

4.3.4. (5-Methyl-2-oxo-1,2-dihydro-indol-3-ilidene)-cyanoacetic acid ethyl ester (12d). Fine dark-red solid, mp 198 °C; 1.82 g (71%) yield. Found: C, 65.44; H, 4.70; N, 10.98. $C_{14}H_{12}N_2O_3$ requires C, 65.62; H, 4.72; N, 10.93%; ν_{max} (KBr) 3267, 2988, 2213, 1716, 1622, 1576, 1485 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 1.31 (3H, t, *J* 8.2 Hz), 2.22 (s, 3H), 2.48 (2H, q, *J* 3.7 Hz), 6.74 (1H, d, *J* 8.9 Hz), 7.27 (1H, d, *J* 7.9 Hz), 7.90 (s, 1H), 10.94 (s, 1H); δ_C (100.61 MHz, DMSO-d_6) 13.759, 59.120 (Et carbons), 24.280 (5-CH_3), 104.250 (ilidene sp^2 carbon $=C(CN)_2$), 118.223 (2C, CN), 121.230, 126.700, 127.132, 128.425, 132.856, 133.280, 164.512 (sp^2 carbons), 162.842, 165.120 (CO sp^2 carbons); MS (EI) *m/z* 256 (100 M^+), 228 (9.0), 212 (5.3), 211 (38.3), 186 (3.2), 185 (12.7), 184 (88.3), 183 (55.4), 182 (9.9), 181 (2.4), 173 (2.6), 161 (3.5), 158 (6.4), 157 (9.9), 156 (28.6), 155 (61.9), 154 (4.1), 153 (3.7), 150 (2.3), 142 (2.2), 141 (3.1), 140 (3.6), 133 (5.5), 130 (2.1), 129 (5.2), 128 (17.8), 127 (8.4), 126 (3.5), 118 (19.9), 101 (13.3), 77 (12), 74 (8.7), 63 (3%).

4.4. General procedures for the synthesis of 4,3′-spiro[(6-amino-5-R-3-methyl-2*H*,4*H*-pyrano[2,3-*c*]-pyrazolo)-2′-oxindole] (4a–h)

Method A. Three-component one-pot procedure. The respective isatins **7a–d** (0.01 mol), triethanolamine (1.3 mL, 0.01 mol) and 5-methyl-2,4-dihydro-pyrazol-3-one **8** (0.98 g, 0.01 mol) in dry ethanol (10.0 mL) were gradually added to malonodinitrile **9** solution (0.66 g, 0.01 mol) or cyanoacetic acid ethyl ester **10** (1.1 mL, 0.01 mol) in dry ethanol (5.0 mL). When nitrile **9** was used the reaction mixture was heated gently until the contents of the flask dissolved and then stirred at room temperature until the colourless precipitate of compounds **4a–d** was obtained (usually 1 h). When compound **10** was used, the resulting reaction mixture was refluxed for 2 h. The mixture was allowed to form the precipitate of **4e–h**. The resulting precipitates of compounds **4a–g** were filtered, washed with hexane or recrystallized from the ethanol and DMF mixture (1:1) and then dried.

Method B. Synthesis using 3-cyanomethyliden-2-oxindoles. A solution of 3-cyanomethyliden-2-oxindole (0.01 mol) **11a–d** or **12a–d** and 0.98 g, 0.01 mol of compound **8**, and triethanolamine (1.3 mL, 0.01 mol) was refluxed in dry ethanol (20.0 mL). When **11a–d** was used the reaction mixture was refluxed for 1 h and in case of synthesis with **12a–d** nitriles—for 2 h. The resulting precipitates of **4a–g** were treated as mentioned in method A.

The yields for the synthesized compounds **4a–h** are presented in Table 1.

4.4.1. 4,3′-Spiro[(6-amino-5-cyano-3-methyl-2*H*,4*H*-pyrano[2,3-*c*]pyrazolo)-2′-oxindole] (4a). Fine colourless needles, mp 175–177 °C. Found: C, 61.23; H, 3.66; N, 24.03. $C_{15}H_{11}N_5O_2$ requires C, 61.43; H, 3.78; N, 23.88%. UV–vis (EtOH) λ_{max}: 245 nm (ε 6992); ν_{max} (KBr) 3313, 3159, 3010, 2973, 2938, 2902, 2844, 2795, 2725, 2611, 2502, 2182, 1712, 1583, 1488 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 1.5 (s, 3H), 6.98–7.1 (m, 3H), 7.2–7.4 (m, 1H+2H, D_2O exchangeable, NH_2), 10.65 (s, 1H, D_2O exchangeable, NH), 12.25 (s, 1H, D_2O exchangeable, NH); δ_C (100.61 MHz, DMSO-d_6) 9.304 (3-CH_3), 55.256 (quaternary sp^3 carbon), 118.712 (CN), 109.673, 122.503, 124.482, 128.882, 132.637, 134.707, 141.453 (sp^2 carbons), 155.218 (sp^2 β-carbon, pyran), 162.417 (sp^2 α-carbon, pyran), 167.960 (CO 2-oxindolic); MS (EI) *m/z* 293 (22.3 M^+), 267 (27.2), 266 (7.4), 265 (52.6), 264 (100), 250 (6.5), 227 (12.2), 208 (18), 207 (5.7), 199 (13.2), 115 (5.7%).

4.4.2. 4,3′-Spiro[(6-amino-5-cyano-3-methyl-2*H*,4*H*-pyrano[2,3-*c*]pyrazolo)-*N*′-methyl-2′-oxindole] (4b). Fine colourless needles, mp 250 °C. Found: C, 62.34; H, 4.19; N, 22.83. $C_{16}H_{13}N_5O_2$ requires C, 62.53; H, 4.26; N, 22.79%. UV–vis (EtOH) λ_{max}: 256 nm (ε 16,649); ν_{max} (KBr) 3380, 3329, 3130, 2189, 1703, 1641, 1605, 1590, 1521, 1495, 1469 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 1.52 (s, 3H), 3.45 (s, 3H), 6.9–7.12 (m, 3H), 7.20–7.49 (m, 1H+2H, D_2O exchangeable, NH_2), 12.15 (s, 1H, D_2O exchangeable, NH); δ_C (100.61 MHz, DMSO-d_6) 9.275 (3-CH_3), 43.930 (NCH_3), 54.837 (quaternary sp^3 carbon), 118.418 (CN), 108.855, 123.063, 124.021, 128.917, 131.798, 134.575, 142.833 (sp^2 carbons), 155.092 (sp^2 β-carbon, pyran), 162.446 (sp^2 α-carbon, pyran), 176.123 (CO 2-oxindolic); MS (EI) *m/z* 307 (12 M^+), 281 (9.8), 279 (21.1), 278 (66.5), 264 (9.7), 250 (5.5), 242 (14.6), 241 (100), 240 (22), 225 (6.4), 224 (6.6), 222 (18.2), 213 (7.6), 209 (9.2), 184 (6.6), 154 (5.8%).

4.4.3. 4,3′-Spiro[(6-amino-5-cyano-3-methyl-2*H*,4*H*-pyrano[2,3-*c*]pyrazolo)-*N*′-benzyl-2′-oxindole] (4c). Fine colourless cubes, mp 210 °C. Found: C, 68.71; H, 4.42; N, 18.36. $C_{22}H_{17}N_5O_2$ requires C, 68.92; H, 4.47; N, 18.27%. UV–vis (EtOH) λ_{max}: 254 nm (ε 21,544); ν_{max} (KBr) 3390, 3234, 3150, 2200, 1708, 1636, 1593, 1488, 1468, 1454 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 1.45 (s, 3H), 4.9 (s, 2H), 6.9–7.2 (m, 3H), 7.22–7.48 (m, 8H), 12.33 (s, 1H, D_2O exchangeable, NH); δ_C (100.61 MHz, DMSO-d_6) 8.962 (3-CH_3), 47.053 (CH_2), 55.023 (quaternary sp^3 carbon), 118.599 (CN), 96.164, 109.263, 123.231, 124.362, 127.427, 128.464, 128.883, 131.785, 134.709, 136.021, 141.947 (sp^2 carbons), 155.195 (sp^2 β-carbon, pyran), 162.537 (sp^2 α-carbon, pyran), 176.540 (CO 2-oxindolic); MS (EI) *m/z* 383 (6.8 M^+), 392 (16), 355 (3.2), 292 (16.5), 285 (5.3), 258 3.9, 257 (16.7), 244 (4.1), 243 (4.6), 239 (11.4), 237 (5.2), 233 (7), 231 (12.9), 227 (12.1), 226 (90), 211 (3.7), 198 (8.7), 183 (8.1), 140 (12.6%).

4.4.4. 4,3′-Spiro[(6-amino-5-cyano-3-methyl-2*H*,4*H*-pyrano[2,3-*c*]pyrazolo)-5′-methyl-2′-oxindole] (4d). White powder, mp 178–180 °C. Found: C, 62.21; H, 4.08; N, 22.92. $C_{16}H_{13}N_5O_2$ requires C, 62.53; H, 4.26; N, 22.79%.

UV–vis (EtOH) λ_{max}: 255 nm (ε 15,392); ν_{max} (KBr) 3345, 3144, 3022, 2946, 2922, 2184, 1899, 1705, 1645, 1624, 1608, 1582, 1518, 1493 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 1.5 (s, 3H), 2.2 (s, 3H), 6.77 (1H, d, *J* 7.9 Hz), 6.83 (s, 1H), 7.02 (1H, d, *J* 7.3 Hz), 7.18 (s, 2H, D_2O exchangeable, NH_2), 10.47 (s, 1H, D_2O exchangeable, NH), 12.25 (s, 1H, D_2O exchangeable, NH); δ_C (100.61 MHz, DMSO-d_6) 8.980 (3-CH_3), 20.558 (5′-CH_3), 55.419 (quaternary sp^3 carbon), 118.648 (CN), 95.471, 109.301, 124.828, 129.038, 131.296, 132.744, 134.619, 138.892 (sp^2 carbons), 155.118 (sp^2 β-carbon, pyran), 162.273 (sp^2 α-carbon, pyran), 177.789 (CO 2-oxindolic); MS (EI) *m/z* 307 (9.6 M^+), 327 (5.40), 282 (13.7), 281 (23), 252 (9.5), 150 (100), 151 (7.7), 149 (29.7), 148 (8.3), 132 (4.8), 120 (4%).

4.4.5. 4,3′-Spiro[(6-amino-5-carbethoxy-3-methyl-2*H*,4*H*-pyrano[2,3-*c*]pyrazolo)-2′-oxindole] (4e). White scales, mp 170–172 °C. Found: C, 59.83; H, 4.60; N, 16.69. $C_{17}H_{16}N_4O_4$ requires C, 60.00; H, 4.74; N, 16.46%. UV–vis (EtOH) λ_{max}: 210 nm (ε 25,812), 243 (25,225), 249 (22,090), 295 (3626), 410 (803); ν_{max} (KBr) 3376, 3148, 1692, 1612, 1470, 1385, 1337 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 0.75 (3H, t, *J* 6.3 Hz), 1.52 (s, 3H), 3.12 (s, 3H), 3.55 (2H, q, *J* 6.2 Hz), 6.98–7.1 (m, 3H), 7.2–7.4 (m, 1H +2H, D_2O exchangeable, NH_2), 10.71 (s, 1H, D_2O exchangeable, NH), 12.23 (s, 1H, D_2O exchangeable, NH); δ_C (100.61 MHz, DMSO-d_6) 8.998 (3-CH_3), 13.107, 47.035 (Et carbons), 55.605 (quaternary sp^3 carbon), 74.181, 97.042, 108.591, 121.525, 122.521, 127.186, 134.562, 136.556, 141.823 (sp^2 carbons), 154.272 (sp^2 β-carbon, pyran), 162.273 (sp^2 α-carbon, pyran), 177.077 (CO 2-oxindolic), 179.507 (CO ester); MS (EI) *m/z* 340 (15 M^+), 267 (35), 268 (12.3), 264 (52.6), 263 (100), 250 (6.5), 227 (12.2), 208 (18), 207 (5.7), 199 (13.2), 153 (8.9), 152 (7.1), 142 (7.8), 140 (14.2), 137 (7.5), 128 (10.8), 127 (12.1), 126 (6.2),114 (9.6),112 (5.7%).

4.4.6. 4,3′-Spiro[(6-amino-5-carbethoxy-3-methyl-2*H*,4*H*-pyrano[2,3-*c*]pyrazolo)-*N*′-methyl-2′-oxindole] (4f). Fine colourless prisms, mp 193–195 °C. Found: C, 61.05; H, 5.14; N, 15.83. $C_{18}H_{18}N_4O_4$ requires C, 61.01; H, 5.12; N, 15.81%. UV–vis (EtOH) λ_{max}: 268 nm (ε 17,454); ν_{max} (KBr) 3514, 3368, 3252, 2980, 2904, 2361, 1695, 1609, 1543, 1492, 1477, 1399, 1372, 1354 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 0.61 (3H, t, *J* 6.7 Hz), 1.52 (s, 3H), 3.12 (s, 3H), 3.75 (2H, q, *J* 6.8 Hz), 6.8–7.10 (m, 3H), 7.22 (1H, t, *J* 7.6 Hz), 8.10 (s, 2H, D_2O exchangeable, NH_2), 12.27 (s, 1H, D_2O exchangeable, NH); δ_C (100.61 MHz, DMSO-d_6) 8.898 (3-CH_3), 13.375, 58.489 (Et carbons), 55.988 (quaternary sp^3 carbon), 46.567 (NCH_3), 73.873, 96.860, 107.427, 122.207, 122.281, 127.411, 134.496, 135.696, 143.123 (sp^2 carbons), 154.235 (sp^2 β-carbon, pyran), 162.792 (sp^2 α-carbon, pyran), 167.911 (CO 2-oxindolic), 177.717 (CO ester); MS (EI) *m/z* 354 (8.29 M^+), 282 (13.7), 281 (100), 254 (7.5), 253 (62.5), 251 (6.7), 210 (7.1), 209 (5.9), 195 (6.3), 185 (7.1), 184 (19.3), 183 (14.3), 182 (6.1), 181 (7.7), 180 (7.9), 179 (8.9), 169 (12.1), 168 (11.5), 167 (12.9), 166 (9.0), 156 (9.0), 155 (14.3), 154 (18.3), 153 (8.9), 152 (7.1), 141 (7.8), 140 (14.2), 139 (7.5), 128 (10.8), 127 (12.1), 126 (6.2), 115 (5.5%).

4.4.7. 4,3′-Spiro[(6-amino-5-carbethoxy-3-methyl-2*H*,4*H*-pyrano[2,3-*c*]pyrazolo)-*N*′-benzyl-2′-oxindole] (4g). White powder, mp 125–128 °C. Found: C, 66.70; H, 5.26; N, 13.09. $C_{24}H_{22}N_4O_4$ requires C, 66.97; H, 5.15; N, 13.02%. UV–vis (EtOH) λ_{max}: 423 nm (ε 256,000), 518 (10,400); ν_{max} (KBr) 3276, 2978, 1676, 1612, 1546, 1485, 1466, 1397 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 0.55 (3H, t, *J* 6.7 Hz,), 1.00 (s, 3H), 3.28 (2H, q, *J* 7.1 Hz), 4.50 (s, 2H), 6.9–7.2 (m, 3H), 7.22–7.48 (m, 6H), 7.85 (s, 2H, D_2O exchangeable, NH_2), 11.85 (s, 1H, D_2O exchangeable, NH); δ_C (100.61 MHz, DMSO-d_6) 9.421 (3-CH_3), 13.045, 58.489 (Et carbons), 43.117 (CH_2), 55.654 (quaternary sp^3 carbon), 98.253, 110.245, 124.231, 125.321, 127.445, 128.962, 129.758, 132.987, 134.201, 136.235, 142.924 (sp^2 carbons), 155.195 (sp^2 β-carbon, pyran), 162.439 (sp^2 α-carbon, pyran), 168.319 (CO 2-oxindolic), 176.654 (CO ester); MS (EI) *m/z* 430 (30 M^+), 358 (13.1), 357 (57.3), 340 (15.5), 339 (62), 333 (15.2), 332 (51.9), 330 (21.7), 329 (79.8), 319 (19.8), 318 (46.8), 317 (86.9), 303 (19.0), 260 (24.1), 258 (24.7), 250 (19.6), 251 (11.8), 249 (100), 239 (15.6), 238 (27.9), 232 (11.7), 231 (19.4), 230 (15.9), 229 (13.6), 226 (65.9), 180 (9.9), 168 (9.9), 140 (14.2%).

4.4.8. 4,3′-Spiro[(6-amino-5-carbethoxy-3-methyl-2*H*,4*H*-pyrano[2,3-*c*]pyrazolo)-5′-methyl-2′-oxindole] (4h). Fine colourless needles, mp 182–184 °C. Found: C, 60.81; H, 5.26; N, 16.1. $C_{18}H_{18}N_4O_4$ requires C, 61.01; H, 5.12; N, 15.81%. UV–vis (EtOH) λ_{max}: 213 nm (ε 21,488), 247 (31,693), 300 (4068), 421 (946); ν_{max} (KBr) 3413, 3347, 3199, 3027, 2923, 2562, 1711, 1675, 1627, 1598, 1530, 1491, 1364 cm^{-1}; δ_H (200 MHz, DMSO-d_6) 0.82 (3H, t, *J* 6.4 Hz), 1.5 (s, 3H), 2.2 (s, 3H), 3.70 (2H, q, *J* 6.8 Hz), 6.70 (m, 2H), 7.2 (1H, d, *J* 6.9 Hz), 7.25 (s, 2H, D_2O exchangeable, NH_2), 10.60 (s, 1H, D_2O exchangeable, NH), 12.30 (s, 1H, D_2O exchangeable, NH); δ_C (100.61 MHz, DMSO-d_6) 8.976 (3-CH_3), 13.589, 58.489 (Et carbons), 20.983 (5′-CH_3), 55.988 (quaternary sp^3 carbon), 96.235, 112.206, 125.728, 130.045, 131.296, 132.744, 134.619, 138.892, 143.123 (sp^2 carbons), 154.235 (sp^2 β-carbon, pyran), 162.792 (sp^2 α-carbon, pyran), 167.923 (CO 2-oxindolic), 178.715 (CO ester); MS (EI) *m/z* 354 (58 M^+), 330 (5.6), 282 (13.7), 273 (6.9), 255 (12), 254 (7.5), 253 (62.5), 241 (6.7), 210 (7.1), 210 (5.9), 195 (6.3), 186 (7.1), 184 (19.3), 183 (14.3), 182 (6.1), 180 (7.9), 179 (8.9), 169 (12.1), 168 (11.5), 167 (12.9), 166 (9.0), 156 (9.0), 155 (14.3), 154 (18.3), 153 (8.9), 152 (9.1), 151 (11.8), 140 (16.2), 139 (5.5), 128 (15.8), 127 (12.1), 125 (6.9), 114 (12.3%).

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